ClinGen Inherited Cardiomyopathy Expert Panel (CMP-EP)

Modified ACMG/AMP Classification Rules for *MYH7*

SUMMARY OF CLASSIFICATION CRITERIA

Pathogenic Criteria		
Rule		**Rule Description**
STRONG	PS1	Different nucleotide change (same amino acid) as a previously established pathogenic variant
	PS2	*De novo (*paternity confirmed) in a patient with disease and no family history
	PS3	Functional studies of mammalian knock-in models supportive of a damaging effect on the gene or gene product
	PS4	Prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls -OR- Variant identified in ≥15 probands with consistent phenotypes
	PP1_Strong	Variant segregates with ≥7 meioses
MODERATE	PM1	Hotspot/est. functional domain (amino acids 181-937) without benign variation
	PM2	Absent/extremely rare (<0.004%) from large population studies
	PM4	Protein length changes due to in-frame deletions/insertions of any size in a non-repeat region or stop-loss variants
	PM5	Missense change at an amino acid residue where a different missense change previously established as pathogenic
	PM6	Confirmed *de novo* without confirmation of paternity
	PVS1_Moderate	Null variant in gene with evidence supporting LOF as disease mechanism
	PS4_Moderate	Variant identified in ≥6 probands with consistent phenotypes
	PP1_Moderate	Variant segregates in ≥5 meioses
SUPPORTING	PP1	Variant segregates in ≥3 meioses
	PP3	Multiple lines of computational evidence support a deleterious effect on the gene or gene product
	PS4_Supporting	Variant identified in ≥2 probands with consistent phenotypes

Benign Criteria		
Rule		**Rule Description**
SA	BA1	Allele frequency is ≥0.1% based on the filtering allele frequency (FAF) in ExAC
STRONG	BS1	Allele frequency is ≥0.02% based on the filtering allele frequency (FAF) in ExAC provided there is no conflicting information
	BS3	Functional studies of mammalian knock-in models supportive of no damaging effect on protein function or splicing
	BS4	Non-segregation in affected members of a family
SUPPORTING	BP2	Observed as comp het (in trans) or double het in genes with overlapping function (e.g. sarcomere genes) without increased disease severity -OR- Observed in cis with a pathogenic variant in any inheritance pattern
	BP4	Multiple lines of computational evidence suggest no impact on gene or gene product
	BP5	Variant found in a case with an alternate molecular basis for disease
	BP7	A silent variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site -AND- the nucleotide is not highly conserved